71. The method of claim 70, wherein said heart disease is a heart insufficiency, dilative or hypertrophic cardiomyopathy, dystrophinopathy, vessel disorder, high blood pressure, atherosclerosis, stenosis of a blood vessel, or restenosis of a blood vessel.

72. A pharmaceutical composition comprising a recombinant virus vector of claim 52 and a pharmaceutically acceptable carrier.

73. The pharmaceutical composition according to claim 72 that expresses said nucleic acid to be expressed specifically in the heart or the heart cavity of a subject to which said composition is administered.--

REMARKS

The Office Action of October 14, 1999, presents the examination of claims 1-3, claims 4-19 being objected to as being presented in improper form as being multiply dependent upon prior multiple-dependent claims.

Applicants have canceled claims 1-19, presenting the subject matter as new claims 20-68. Claims 20-68 include the subject matter of claims 4-19; therefore, the next Office Action will be the first examination of the claimed subject matter on the merits.

Accordingly, Applicants point out that the Examiner cannot make the next Office Action final.

Claim Objections and Rejections Under 35 U.S.C. §§ 101 and 112, Second Paragraph

Claims 4-19 were objected to as being multiply dependent from prior multiple-dependent claims. Dependent claims among claims 20-68 are presented in properly dependent form.

Claims 1-3 were rejected under 35 U.S.C. § 101 as reciting non-statutory subject matter in the form of "a working model". New claims 20-68 properly claim either a composition or a method, thus overcoming this rejection.

Claims 1-3 were rejected under 35 U.S.C. § 112, second paragraph, for the recitation of "a working model" as the subject matter of the claims, for misspelling of "ribozyme", for inclusion of embedded ranges, and for use of the indefinite article "a" to begin the preamble of dependent claims. New claims 20-68 correct all of these defects of the claims, thus obviating this rejection.

Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 1-3 were rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement of the making or of the alleged utility of the invention. These claims are also rejected under the

same statute for alleged lack of written description sufficient to demonstrate that the inventors had possession of the claimed invention. These rejections are respectfully traversed as they might be applied to the new claims. Applicants submit that these rejections should not be applied to the present claims.

Enablement

The Examiner grounds the enablement rejection on two bases. First, the Examiner indicates that claims directed to ribozyme and antisense embodiments are not enabled. Second the Examiner indicates that claims directed to methods for gene therapy are not enabled.

First, Applicants point out that the present claims are directed to many different embodiments of the invention:

1. Constructs and vectors comprising regulatory elements driving heart-specific or heart cavity-specific expression of a desired gene;
2. Methods for making such constructs and vectors;
3. Pharmaceutical compositions comprising such constructs or vectors;
4. Methods for delivery of a nucleic acid to be expressed in the heart or heart cavity by administration of a construct or vector;

5. Methods for therapy of a disease by administration of a pharmaceutical composition comprising such constructs or vectors.

Applicants submit that embodiments 1, 2 and 4 should be free of any concerns expressed by the Examiner regarding "gene therapy". Applicants assert that the construction of any particular recombinant DNA construct is well within the skill of the ordinary practitioner of the art given the pieces of nucleic acid to assemble. Applicants further assert that working examples 8-12 and the data shown in Figures 5C, 8A and 8B demonstrate that the constructs of the invention are effective for delivery of a gene to heart tissue of an animal to produce heart-specific or heart cavity-specific expression of a desired nucleic acid.

As to the embodiments that recite an antisense nucleic acid as the desired nucleic acid to be expressed, Applicants point out that the present invention does not lie in the design of a particular antisense nucleic acid. The invention lies in the construct for obtaining heart-specific or heart cavity-specific expression of any desired nucleic acid that has already been selected by the practitioner. Whatever the difficulties may be that need to be overcome to design an appropriate antisense nucleic acid to be expressed, these issues are outside purview of the present invention. The practitioner of the art is presumed to know the difficulties

associated with antisense technologies and also to know how to address them. The present specification need not, and preferably does not, describe what is already known in the art. *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81, 94 (Fed. Cir. 1986).

Of course, the present invention can also be applied when appropriate to providing heart-specific or heart cavity-specific expression of nucleic acids encoding antisense or ribozyme products (or proteins) that are developed later. This aspect of the invention is reflected in the generic recitation of the "antisense or ribozyme" (or "proteinaceous gene product") that is to be expressed.

As to the gene therapy embodiments of the invention, included embodiments in categories 3 and 5 above, Applicants acknowledge the difficulties in accomplishing successful gene therapy that are described by the Examiner. However, the Examiner must understand that the present invention is intended to specifically address one of the problems she has noted. Applicants note that Anderson is quoted as indicating that gene therapy is hampered by "poor delivery systems". Applicants assert that the present invention provides an effective delivery system. This assertion is supported by evidence provided by working examples set forth in the specification showing expression of a desired gene in a desired tissue after administration of a construct according to the invention to an animal.

Applicants note that expression of the desired luciferase protein was detected by activity measurement in Examples 8 and 12 five days after administration of the recombinant virus. The animal experiments set forth in the specification also demonstrate effective targeting of expression of a therapeutic gene product to a desired tissue, in this case, the heart or heart cavity.

Again, the issue of what might be a protein that should be expressed to accomplish a therapeutic effect and how the gene encoding that protein should be designed to accomplish a desired level of expression and desired stability of expression is up to the practitioner. Different therapeutic objectives will require different designs for the gene to be expressed. In general, Applicants are not claiming therapy for specific diseases. Applicants reiterate that the asserted utility of the present invention is to achieve effective delivery and tissue specificity of any desired gene.

As to the specific diseases recited in e.g., claim 41, Applicants assert that the state of the art suggests a connection between the diseases listed and the specific proteins to be expressed, e.g., as stated in claim 33. For instance it is clear that dystrophinopathy represents a defect in dystrophin protein expression. Also, the level of nitric oxide in blood vessel endothelial cells has been linked to blood pressure regulation.

Similarly, the treatment of various heart diseases by administration of drugs working through the β adrenergic receptor, so-called "beta blockers", is well-known.

The Examiner is reminded that the purpose of the patent system is to promote progress in the useful arts. That progress might be incremental. Certain technologies are not going to be achieved all at once. That barriers to achieving some technological advances exist is not a reason to deny patent claims to inventions that address some, but not all, of the barriers to such a desired technical advance. Achieving the goal of successful gene therapy will require developments like the present invention, which provide good delivery systems, as well as additional inventions related to design of specific genes that are to be delivered using the present invention to treat specific diseases. The Examiner should not reject claims to inventions addressing one part of gene therapy technology based upon problems to be solved in a different part of the technology.

Written Description

The rejection grounded on alleged lack of written description is related first to the antisense or ribozyme problems described above. Applicants submit that their comments with respect to enablement of the antisense and ribozyme embodiments of the invention apply as well, or with more force, to the written description basis. In

particular, the specification is not required to describe in detail aspects of the invention within the knowledge of the ordinarily-skilled practitioner of the invention or within the prior art. As explained above, it is Applicants' position that the details of designing antisense or ribozyme nucleic acids to be expressed using the present invention are either known in the prior art or are within the skill of the practitioner of the invention, in that it is a design choice of the practitioner as to what nucleic acid should be expressed using the present invention.

The Examiner also presents a "representative number of species" argument. The Examiner argues that Applicants' working examples using MLC-2/luciferase constructs does not show a number of species sufficient to support claims to MLC-2/antisense or ribozyme constructs. The Examiner is first reminded that the specification is not limited to the working examples.

Second, Applicants submit that the specification is sufficient regarding the species recited. The invention is claimed in terms of constructs comprising MLC-2 regulatory elements linked to any "nucleic acid to be expressed". Applicants describe three "species" of nucleic acids: those encoding proteins, those encoding antisense nucleic acids and those encoding ribozymes. All of these are linked by the common structural feature of being nucleic acids.

For all of the above reasons, Applicants submit that the specification is fully enabling of practice of the invention as described by the present claims. Accordingly, the standing rejections of claims 1-3 under 35 U.S.C. § 112, first paragraph, should not be applied to the present claims.

Rejections Over Prior Art

Claims 1-3 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over any one of the following references: Franz et al., Arnold et al., Knowleton et al., Shubeita et al., Navankasattusas et al., Thornburn et al., or Goswami et al., in view of Ricigliano et al. and Zaia et al. This rejection is respectfully traversed as it might be applied to the present claims. Applicants submit that this rejection should not apply to the present claims.

The Examiner interprets claims 1-3 as being directed to a nucleic acid construct comprising a MLC-2 promoter linked to a sequence coding for an antisense molecule or a ribozyme. Applicants first clarify that the present claims are a bit broader in that the recited regulatory elements can also be linked to a polynucleotide encoding a protein product or any other sort of nucleic acid to be expressed. The present claims also recite that the construct comprises specific regulatory elements that result in heart-specific or heart cavity-specific expression of a desired gene.

On the other hand, the primary references cited by the Examiner describe either one or more regulatory elements or a large fragment of DNA purported to confer heart-specific expression to a desired nucleic acid linked to the regulatory elements. However, none of the references cited appear to describe or suggest the specific combination of regulatory elements recited in the present claims. In particular, none of the cited references appears to describe the MLE1 element of claim 20. None of the references suggest that heart-specific or heart cavity-specific expression can be achieved using only the elements recited in claim 20. The Franz reference, which might be the closest prior art, shows heart-specific expression using a 2.1 kb portion of the upstream region of the MLC-2 gene. However, Franz et al. do not specifically describe a MLE1 element. Furthermore, Franz et al. ascribe the heart-specific expression mostly to a CSS sequence, explaining that deletion of the CSS sequence results in expression of marker genes in skeletal muscle (*see*, p. 636, first col., lines 18-22). Thus, Franz et al. do not disclose or suggest the present invention.

The secondary references are cited only to provide teachings of antisense or ribozyme nucleic acids and for the concept that such nucleic acids can be expressed under the control of tissue-specific promoters. The Examiner does not assert that any of the secondary

references describe or suggest a heart-specific or heart cavity-specific gene regulatory element.

Applicants submit that the Examiner fails to make a *prima facie* case of obviousness of the presently claimed invention. As pointed out above, none of the references discloses or suggests the specific combination of regulatory elements recited in claim 20. As none of the references individually discloses all of the elements recited, no combination of the references can disclose or suggest the combination of the regulatory elements recited. Thus, the invention of claims 20-72 is not *prima facie* obvious over the cited references, and the present rejection should not be applied to the present claims.

If there are any minor matters precluding allowance of the application which may be resolved by a telephone discussion, the Examiner is respectfully requested to contact Mark J. Nuell, Ph.D. (Reg. No. 36,623) at (703) 205-8000.

Pursuant to 37 C.F.R. § 1.17 and 1.136(a), Applicants respectfully petition a one (1) month extension of time for filing a response in connection with the present application. The required fee of $110.00 is attached hereto.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees

required under 37 C.F.R. §§1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

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